Medical Comorbidity and Late Life Depression: What is Known and What are the Unmet Needs?

Mary Charlson and Janey C. Peterson

Depression is an important problem in older patients with multiple medical problems, where the under-recognition and undertreatment of depression is especially common. A large number of studies assessing the relationship between depression and medical burden have focused on patients with cardiac disease, and recent research has focused on the role of depression as an independent risk factor for cardiac disease, mortality, and functional status in elderly patients. In particular, among coronary bypass surgery patients, depressive symptoms were found to occur most commonly in those with the highest comorbidity. In the treatment of depression in older adults, both pharmacologic and psychosocial interventions have shown promise, but such treatments need to be tested to determine whether mortality and functional status are affected. From a methodological perspective, new studies will need to control for comorbid disease, as many previous studies suggesting depression as a risk factor for mortality in cardiovascular patients have not consistently done so.


Key Words: Comorbidity, depression, elderly patients

Introduction

The adverse impact of late-life depression on mortality, morbidity, and function as well as service utilization is well known to geriatric psychiatrists. Depressed elderly patients often have chronic comorbid conditions such as asthma, coronary artery disease, cancer, diabetes, and hypertension (Wells et al 1989). The common simultaneous occurrence poses separate issues from the clinical and methodologic perspectives. Clinically, the presence of serious comorbid disease may be a barrier to the diagnosis of depression, with symptoms attributed to the comorbid disease and not to depression. Further, comorbidity may complicate treatment of depression in older adults. Methodologically, since both comorbidity and depression may have an adverse impact on long-term outcomes, with increased mortality and morbidity, decreased function, and increased resource utilization, the potential for confounding is considerable.

The objective of this paper is to review what is known about medical comorbidity and late-life depression, and to consider the extent to which comorbidity has been controlled for in studies of late-life depression in medical outpatients, inpatients, and patients with specific comorbid diseases, including cancer and cardiovascular disease.

The hypothesis of this paper is that patients with the greatest comorbidity are at especially high risk for depressive symptoms and poor outcomes, and that if comorbidity is not adequately measured there is important potential for confounding.

Comorbidity and Depression in Outpatients: Diagnosis and Resource Utilization

Older patients treated in primary care settings, the vast majority of whom have comorbid illnesses, have 10%–25% rates of depression (Spitzer et al 1994; Simon 1995; Unutzer et al 2000; Callahan et al 1994; Luber et al 2001). In fact, there may be a direct relationship between comorbidity and depression. In a large study of HMO patients, increasing rates of depression were found with increasing medical comorbidity (Unutzer et al 1997).

Despite the increased prevalence of depression in the medically ill elderly, primary care physicians fail to diagnose depression in as many as half of their elderly depressed patients (Goldman et al 1999). While many factors including patient and physician attitudes may influence the missed diagnosis (Von Korff et al 2001), comorbidity undoubtedly plays a major confounding role. Symptoms of coronary artery disease, asthma, cancer and diabetes may mimic depressive symptoms in elderly patients (Nelson 2001; Shah and Harris 1997), and physicians may assume that patients’ symptoms are attributable to medical comorbidity rather than depression (Luber et al 2000; Unutzer et al 2000; Lin et al 2000).

In this way, comorbidity may obscure the diagnosis of depression. Further, the methods used for diagnosis of depression, including self report scales such as the CES-D, (Weissman...
et al 1977) the Beck Depression Inventory (BDI) (Beck 1961), the Geriatric Depression Scale (GDS) (Yesavage et al 1983), the Zung (Zung 1965), the MMPI-D or MMPI-Dep (Butcher et al 1989), or other similar instruments may yield different estimates of the prevalence of depression than the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer 1978), the DIS (Robins et al 1981), the Hamilton Depression Rating Scale (HDRS) (Hamilton 1967), or structured interviews. Instruments such as the CES-D, which include somatic symptoms, may overestimate the prevalence of depression in the elderly who are medically ill.

Comorbidity can also confound the evaluation of the impact of depression on outcomes in outpatients. For example, in outpatients, while depression in elderly patients has been shown to lead to a higher rate of utilization of health services (Callahan et al 1994; Luber et al 2001; Ciechanowski et al 2000), comorbidity has similarly been shown to lead to increased utilization of services (Luber et al 2001). Thus, both depression and comorbidity predict increased longitudinal costs of care in older primary care patients (Unutzer 1997; Luber et al 2001).

Comorbidity and Depression in Hospitalized Patients: Assessing Long-Term Mortality

Older hospitalized patients have especially high rates of depression. One study using the GDS (Yesavage et al 1983) reported that 34% of older inpatients had depressive symptoms (Covinsky et al 1999). Another study using structured interviews found that half of inpatients were depressed (Koenig 1997); almost 22% of these patients had major depression, while an additional 28% had minor depression (Koenig 1997; Pouget et al 2000).

Rates of depressive symptoms increase with increasing comorbidity. For example, patients with six or more depressive symptoms had higher comorbidity scores (Covinsky et al 1999). Further, comorbidity appears to be greater with major depression. Patients with major depression have been shown to have more comorbidity than those with minor depression or no depression (Koenig 1997). Thus, in older medical patients, depression and comorbid disease both commonly occur together, and patients with more comorbid disease are more likely to be depressed. The greater the comorbidity, then, the greater the likelihood of depression (Roach et al 1998; Covinsky et al 1999; Koenig 1988; Koenig 1997).

Among elderly hospitalized patients, both comorbidity and depression predicted long-term survival (Koenig 1997; Roach et al 1998). In one study, the total burden of comorbid disease contributed more to the mortality rate than depressive symptoms (Covinsky et al 1999). However, the excess mortality rate associated with depressive symptoms was greater than that conferred by one additional comorbid condition (Covinsky et al 1999). In another study that focused on seriously ill patients, the number of comorbid illnesses, depressed mood, age, and function all predicted mortality (Roach et al 1998). Thus, among older hospitalized patients, both depressive symptoms and more comorbidity predict higher long-term mortality controlling for comorbidity, illness severity, and physical function (Covinsky et al 1999; Roach et al 1998). (For a summary of studies of medical inpatients and outpatients and the relationship of depression to outcomes, see Table 1.)

Comorbidity and Depression: Assessing Functional Status

Comorbidity and depression have both been associated with decreased functional status. For example, depressed patients with coronary artery disease have decreased function and lower perceived quality of life than nondepressed patients (Spertus et al 2000). In both asthma and diabetes, depression has an independent adverse impact on function (Mancuso et al 2000; Ciechanowski et al 2000). Among patients with other comorbid medical conditions, both depression and comorbidity have an independent, additive adverse impact on patients’ functioning (Wells et al 1989; Hays et al 1995; Geerlings et al 2001).

The relationship between depression and comorbidity in older adults and poor functional outcomes may be the result of limitations imposed by the illness, or it may be the result of depressed patients’ perceptions or expectations regarding their possible function (Berkman 1986). For example, patients with low self-efficacy were more likely to have depression following major surgery, and poorer functional status (Kurlowicz 1998). In summary, depression and comorbidity have a unique and likely additive adverse impact on function (Wells et al 1989).

Specific Comorbid Diseases and Depression

DEPRESSION AND CANCER. While depression may be underdiagnosed in medically ill patients in outpatient and inpatient settings, it is probably even more often missed in patients with cancer. Neurovegetative symptoms due to depression may easily be misattributed to cancer (McDaniel et al 1995). Among cancer patients, 25%–38% rates of major depression have been reported, with an additional 19% having depressive symptoms (Kathol et al 1990; McDaniel et al 1995; Massie 1990). Given these realities, the relationship between cancer, depression, and outcome has remarkably little data.

The independent impact of depression on long-term outcomes in cancer patients is not clearly documented (Trijsburg et al 1992). Several small studies have sug-
gested improvement in survival with treatment of depression (Fawzy et al 1993), and others have suggested improved quality of life (Costa et al 1985; Evans et al 1988). Compliance with cancer treatment has also been suggested to improve survival (Richardson et al 1990). In contrast, psychologic response to cancer has been suggested as a significant predictor of long-term survival (Greer 1991; Greer et al 1990; Greer et al 1979); in particular, a helplessness/hopelessness coping style has been shown to be an unfavorable prognostic marker in cancer patients (Greer 1991).

Depression and Other Specific Comorbid Conditions

Depression occurs frequently among patients with chronic illnesses and tends to be persistent (Wells et al 1989). For example, depression is common among diabetic patients (Lustman et al 2000) and predicts symptoms associated with worsening glucose control (Lustman et al 1988). Compliance with cancer treatment has also been suggested to improve survival (Richardson et al 1990). In contrast, psychologic response to cancer has been suggested as a significant predictor of long-term survival (Greer 1991; Greer et al 1990; Greer et al 1979); in particular, a helplessness/hopelessness coping style has been shown to be an unfavorable prognostic marker in cancer patients (Greer 1991).

Table 1. Studies of Medical Inpatients and Outpatients: Relationship of Depression to Outcomes

<table>
<thead>
<tr>
<th>Hospital Inpatients</th>
<th>Age</th>
<th>Follow up (yrs)</th>
<th>Measures</th>
<th>3-yr Mortality (Relative Risk)</th>
<th>Relative Risk</th>
<th>Comorbidity Measured</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covinsky et al 1999</td>
<td>80</td>
<td>3</td>
<td>GDS</td>
<td>1.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>ADL, Cognition</td>
<td>APACHE ADL</td>
</tr>
<tr>
<td>Roach et al 1998</td>
<td>61</td>
<td>4.5</td>
<td>POMS</td>
<td>1.13&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Yes (Number of comorbid illnesses)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Care Patients</th>
<th>Age</th>
<th>Follow up (yrs)</th>
<th>Measures</th>
<th>ER/OPD visits</th>
<th>Costs</th>
<th>Comorbidity Measured</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unutzer et al 2000</td>
<td>73</td>
<td>2</td>
<td>CES-D</td>
<td>—</td>
<td>1.5</td>
<td>Yes</td>
<td>Age Gender</td>
</tr>
<tr>
<td>Luber et al 2001</td>
<td>74</td>
<td>1</td>
<td>Clinical diagnosis</td>
<td>2.1</td>
<td>1.1</td>
<td>Yes</td>
<td>Age Gender</td>
</tr>
<tr>
<td>Simon G 1995</td>
<td>38</td>
<td>1</td>
<td>GHQ and structured interviews</td>
<td>—</td>
<td>2.0</td>
<td>Yes</td>
<td>Age Gender</td>
</tr>
</tbody>
</table>

ADL, activities of daily living; APACHE, Acute Physiology and Chronic Health Evaluation; CES-D, Center for Epidemiologic Studies Depression Screen; ER, emergency room; GDS, Geriatric Depression Scale; GHQ, generalized health questionnaire; HMO, health maintenance organization; OPD, obvious depression; POMS, Profile of mood states.

<sup>a</sup>Hazard ratio.

<sup>b</sup>Increased odds with increased of 1 in POMS score.

DEPRESSION AND CARDIAC DISEASE. Recent studies have begun to evaluate depression as an independent risk factor for cardiac disease (Roos et al 2001). In fact, the literature contains multiple epidemiologic studies that strongly suggest the presence of depression greatly increases the risk for ischemic heart disease in otherwise healthy men and women (Glassman and Shapiro 1998). These epidemiologic studies have used different methods to measure depression and different sampling strategies. Table 2 shows the specific studies, their populations, the follow-up interval, the measure of depression, whether comorbidity was measured, the cardiac outcomes, and confounders. In the Precursors study, participants who reported that they had clinical depression had twice the lifetime rate of coronary heart disease (Ford et al 1998). An increased risk of coronary heart disease in depressed patients has also been reported in National Health and Nutrition Examination Survey I (NHANES I) (Anda et al 1993; Ferketich et al 2000); men and women who had depressive symptoms had increased rates of coronary heart disease over a decade of follow-up (Ferketich et al 2000). A community-based Danish cohort of men and women
followed for 27 years showed that depressed patients also had increased risks for myocardial infarction (Barefoot and Schroll 1996). The Baltimore epidemiologic catchment area (ECA) study also showed a relationship between major depression and subsequent myocardial infarction (Pratt et al 1996). In the Systolic Hypertension in the Elderly Project (SHEP) study, patients older than 60 years with depressive symptoms at baseline had twice the rate of new onset congestive heart failure over five years than nondepressed patients (Abramson et al 2001). Data from the SHEP study has also helped to define the relationship between increased depressive symptoms and subsequent cardiovascular disease in older adults. Older patients who had an increase in depressive symptoms had increased rates of myocardial infarction and stroke (Wassertheil-Smoller et al 1996).

Therefore, depressed patients are at higher risk for developing coronary artery disease, myocardial infarction, and congestive heart failure; however, none of the studies measure comorbidity.

Table 2. Depression, Comorbidity, and Cardiac Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Age</th>
<th>Follow-up Interval Years</th>
<th>Measure of Depression</th>
<th>Relative Risk: Subsequent CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk for CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precursors prospective cohort (Ford et al 1998)</td>
<td>1190 male medical students</td>
<td>26</td>
<td>37</td>
<td>Self-report of clinical depression for over 2 weeks</td>
<td>2.1</td>
</tr>
<tr>
<td>NHANES I (Ferketich et al 2000)</td>
<td>2832 men and women in community</td>
<td>55</td>
<td>8</td>
<td>CES-D</td>
<td>1.7 men</td>
</tr>
<tr>
<td>Danish (Barefoot and Schroll 1996)</td>
<td>710 men and women in community</td>
<td>50</td>
<td>17–27</td>
<td>OBD scale of MMPI</td>
<td>1.3 women (ns)</td>
</tr>
<tr>
<td>ECA (Pratt et al 1996)</td>
<td>1551 men and women in community</td>
<td>13</td>
<td></td>
<td>Major depression</td>
<td>DIS</td>
</tr>
<tr>
<td>SHEP (Abramson et al 2001)</td>
<td>4538</td>
<td>72</td>
<td>4</td>
<td>CES-D</td>
<td>—</td>
</tr>
<tr>
<td>Normative Study on Aging (Sesso et al 1998)</td>
<td>1305 men community dwelling</td>
<td>60</td>
<td>7</td>
<td>MMP12-D</td>
<td>1.5–1.9</td>
</tr>
<tr>
<td>Penninx et al 2001</td>
<td>2847</td>
<td>70</td>
<td>4</td>
<td>CES-D (minor)</td>
<td>DIS (major)</td>
</tr>
<tr>
<td>Mini-Finland Health (Aromaa, Reunanen et al 1994)</td>
<td>2653 men and women (community based)</td>
<td>&gt; 40</td>
<td>8</td>
<td>General Health (GHQ)</td>
<td>Psychiatric Interview</td>
</tr>
<tr>
<td>Vogt et al 1994</td>
<td>1499 HMO members</td>
<td>50</td>
<td>15</td>
<td>Depression index</td>
<td>McFarland</td>
</tr>
<tr>
<td>Wassertheil-Smoller et al 1996</td>
<td>4736</td>
<td>72</td>
<td>4.5</td>
<td>CES-D</td>
<td>3.0 men</td>
</tr>
<tr>
<td>Simonsick et al 1995</td>
<td>3059 men and women with HBPP</td>
<td>65+</td>
<td>3</td>
<td>CES-D</td>
<td>1.8 women</td>
</tr>
<tr>
<td>MI Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berkman et al 1992</td>
<td>194 MI patients</td>
<td>75+</td>
<td>6 months</td>
<td>CES-D</td>
<td>—</td>
</tr>
<tr>
<td>Frasure-Smith et al 1995</td>
<td>222 MI patients</td>
<td>62</td>
<td>1.5</td>
<td>Beck</td>
<td>DIS</td>
</tr>
<tr>
<td>Bush et al 2001</td>
<td>285 MI patients</td>
<td>65</td>
<td>.33</td>
<td>SCID</td>
<td>Beck</td>
</tr>
<tr>
<td>Ladwig et al 1991</td>
<td>560 MI survivors</td>
<td>&gt; 50</td>
<td>6 months</td>
<td>Major depressive disorder</td>
<td>—</td>
</tr>
<tr>
<td>CHF Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murberg et al 1999</td>
<td>119</td>
<td>66</td>
<td>2</td>
<td>Zung</td>
<td>—</td>
</tr>
<tr>
<td>CABG Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carney et al 1988</td>
<td>52</td>
<td>58</td>
<td>1</td>
<td>DIS</td>
<td>—</td>
</tr>
<tr>
<td>Pirraglia et al 1999</td>
<td>237</td>
<td>65</td>
<td>6 months</td>
<td>CES-D</td>
<td>—</td>
</tr>
<tr>
<td>Oxman et al 1994</td>
<td>232</td>
<td>68</td>
<td>6 months</td>
<td>HAM-D</td>
<td>—</td>
</tr>
<tr>
<td>Peterson et al 2002</td>
<td>123</td>
<td>65</td>
<td>3</td>
<td>CES-D</td>
<td>—</td>
</tr>
<tr>
<td>Cardiac Test Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barefoot et al 1996</td>
<td>1250 cath</td>
<td>52</td>
<td>15 (median)</td>
<td>Zung</td>
<td>—</td>
</tr>
<tr>
<td>Herrmann et al 2000</td>
<td>5750 with stress test referral</td>
<td>54</td>
<td>5</td>
<td>HADS</td>
<td>—</td>
</tr>
</tbody>
</table>
Depression and Risk of Mortality

**PATIENTS WITHOUT CARDIAC DISEASE.** Depression has been reported to lead to increased cardiac mortality for patients without cardiac disease at baseline. The Longitudinal Study of the Aging in Amsterdam followed 2847 older adults with an average age of 70 for 4 years. Depression was a risk factor for subsequent cardiac mortality among patients without cardiac disease (Penninx et al 2001). However, the analyses adjusted only for...
stroke, diabetes, lung disease and cancer, but not other comorbidity such as renal disease. Patients with major depression had twice the mortality risk of those with minor depression, but again there was no adjustment for comorbidity (Penninx et al 2001).

Several large studies have evaluated depression as a predictor of all-cause mortality and have reached contradictory conclusions. The mini-Finland study of 2653 community dwellers found that depressed patients had increased mortality, but comorbidity was not taken into account. (Aromaa et al 1994). A study based on the EPESE cohort showed increased mortality in depressed patients, after adjusting for diabetes, myocardial infarction, stroke and cardiac risk factors, but not other comorbid diseases (Simonsick et al 1995). Similarly, the SHEP study found an increased rate of all-cause mortality, but without controlling for comorbidity (Wassertheil-Smoller et al 1996). On the other hand, another 15-year longitudinal study of HMO members that also did not control for comorbidity did not find increased mortality (Vogt et al 1994).

**Patients with Cardiac Disease.** Depressed patients with cardiac disease also have been reported to have higher mortality. After myocardial infarction, patients who experienced major depression in the hospital had increased 6- and 18-month all-cause mortality (Frasure-Smith et al 1993; Frasure-Smith et al 1995). Similarly, after myocardial infarction, older patients had stepwise increases in all-cause mortality with stepwise increases in the BDI (Bush et al 2001). In another study of patients after myocardial infarction, those with major depressive disorder had increased mortality (Ladwig et al 1991). None of these studies controlled for comorbidity in their assessment of mortality. In the one study controlling for comorbidity, depression did not predict all cause mortality, although patients with low emotional support after myocardial infarction had lower 6-month survival (Berkman et al 1992). Small studies of patients with congestive heart failure suggested that depressed patients had higher all-cause mortality, but the differences were not significant when other confounders were taken into account (Murberg et al 1999; Jiang et al 2001).

A study of patients who had cardiac catheterization also showed increased risks for all-cause mortality over a median 15-year follow-up among those who were depressed at baseline (Barefoot and Schroll 1996). Depression was not, however, a predictor of mortality among patients referred for exercise testing (Herrmann et al 2000).

In general, therefore, comorbidity was not taken into account in the studies showing increased all-cause mortality in noncardiac or cardiac patients. Most only adjusted for specific diseases such as diabetes which are also risk factors.

**Depression and Events after Coronary Artery Bypass Graft Surgery**

Between 25%–50% of coronary artery bypass graft (CABG) patients have significant depressive symptomatology preoperatively; depressive symptoms decrease significantly postoperatively and are especially high in older patients (Pirraglia et al 1999; Oxman et al 1994). Only one of the three studies that have found increased nonfatal and fatal cardiovascular events in depressed CABG patients did control for comorbidity (Carney et al 1988; Oxman et al 1994). Controlling for comorbidity, patients who become newly depressed at 6 months after CABG have more subsequent cardiovascular morbidity and mortality at 3 years (Peterson et al 2002).

**An Example of the Relationship between Comorbidity and Depression in Cardiac Patients**

An analysis of CABG surgery patients older than 65 years who participated in a randomized trial of intra-operative hemodynamic management provides an example of the relationship between comorbidity and depression, and the impact on functional status of one group of medically ill older adults. The specific objective of this analysis was to evaluate the impact of medical comorbidity on postoperative depressive symptoms and on functional outcomes.

The randomized trial compared two strategies of intra-bypass blood pressure management and enrolled 412 patients, of whom 205 were 65 years or older. The trial was approved by the institutional review board and all patients provided written informed consent. Preoperative assessments included basic sociodemographic and clinical data. Depressive symptoms were assessed using the CES-D (Weissman et al 1977). Functional status was evaluated using the SF-36 (Stewart et al 1989). In addition, the Charlson comorbidity score, a weighted index designed to measure impact of disease on long-term mortality, was assessed (Charlson et al 1987). The weights for the comorbidity score are shown in Table 3. All patients were re-evaluated at 6 months postoperatively. Since an increase in the CES-D of 5 points predicted increased mortality in the SHEP study, this cutoff was employed to define patients with increased depressive symptoms at 6 months postoperatively (Wassertheil-Smoller et al 1996).

In total, 35% of the 205 older patients had preoperative depressive symptoms (CES-D score ≥ 16), but only 6% were taking antidepressants. Postoperatively, 17% of patients had depressive symptoms, and 9% were treated with antidepressants. Figure 1 shows that patients with greater
comorbidity were more likely to have depressive symptoms preoperatively; only 27% of those with a comorbidity score of 0–1, whereas 42% of those with a score of 2–3 and 44% of those with a score of ≥ 4, had depressive symptoms (p = .029).

Among those without depressive symptoms preoperatively, 14% had a postoperative increase in CES-D more than 5 points. Among those with depressive symptoms preoperatively, over 80% had less depressive symptoms by 6 months postoperatively; however, 8% had an increase in CES-D ≥ 5 points at 6 months postoperatively. Figure 2 shows that the increased depressive symptoms occurred among twice as many patients who had comorbidity scores of 4 or more, whether or not patients had depressive symptoms preoperatively (p = .07).

Figure 3 shows the change in SF-36 score postoperatively, according to whether patients experienced a more than 5-unit increase in CES-D score among patients with a comorbidity score of 4 or more. The majority of patients had significant functional improvement after CABG in all domains, but patients with higher comorbidity were more likely to have functional deterioration. Specifically, patients who did not have a comorbidity score of 4 or more in conjunction with a greater than 5-unit increase in CES-D showed significant improvement in all eight domains of the SF-36 health survey (p = .0001 for all). Conversely, those patients with a high comorbid burden coupled with an increase in CES-D score did not show significant improvement in any domain of the SF-36 health survey. Thus, an increase in CES-D was associated with a worsening of functional status in six domains for those with higher comorbidity.

### Table 3. Charlson Comorbidity Scale

<table>
<thead>
<tr>
<th>Comorbid Conditions</th>
<th>Assigned Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Dementia</td>
<td>1</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>1</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td>1</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes without end organ damage</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes with end organ damage</td>
<td>2</td>
</tr>
<tr>
<td>Any tumor</td>
<td>2</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>2</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>3</td>
</tr>
<tr>
<td>Metastatic solid tumor</td>
<td>6</td>
</tr>
<tr>
<td>AIDS</td>
<td>6</td>
</tr>
</tbody>
</table>

The total score is calculated by adding the weights for all the conditions that a patient has. For example, a 73-year-old man with a previous myocardial infarction, diabetes, and chronic lung disease would have a comorbidity score of 3. A patient with dementia and metastatic solid tumor would have a score of 8.

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Figure 1. Percent of older CABG patients who had depressive symptoms preoperatively according to their comorbidity score and antidepressant treatment. CABG, coronary artery bypass graft; CES-D, Center for Epidemiologic Studies depression symptom scale.

Figure 2. Percent of older CABG patients with a 5-unit increase in CES-D at 6 months postoperatively according to comorbidity score and whether or not they were depressed preoperatively. CABG, coronary artery bypass graft; CES-D, Center for Epidemiologic Studies depression symptom scale.

Figure 3. Change in SF-36 score for older patients with comorbidity score ≥ 4 according to whether they had a 5-point increase in CES-D scores. SF-36, SF-36 health survey; CES-D, Center for Epidemiologic Studies depression symptom scale.
Therefore, preoperative depressive symptoms were more common among CABG patients with the highest comorbidity. Among those with a comorbidity score of 4 or more preoperatively, more than 40% of patients had depressive symptoms. Patients with more comorbidity were more likely to have a 5-unit increase in CES-D postoperatively, regardless of preoperative depression status. A 5-unit increase in depression along with a comorbidity score of 4 or more hindered functional improvement at 6 months.

Theoretical Models of the Relationship between Depression and Comorbid Disease

The presence of medical illness has been reported to increase the risk of depression (Cohen and Rodriguez 1995). One model of the relationship between medical comorbidity and late-life depression describes a reciprocal relationship between depression and medical illness, and it includes four pathways: biological, behavioral, cognitive, and social (Cohen and Rodriguez 1995).

In the case of the first pathway of the reciprocal model (biological), comorbid conditions may have direct biological effects associated with developing depression. One biological cause for late-life depression has been described as vascular depression—that is depression occurring in patients with cerebrovascular or ischemic changes in the brain, related to atherosclerosis, hypertension, or myocardial infarction (Krishnan 2000). Disruption of prefrontal systems or modulating pathways by single or multiple lesions are possible central mechanisms in vascular depression (Alexopoulos et al 1997; Alexopoulos et al 1997). Neurotransmitter changes following ischemia may be related to depression (Alexopoulos et al 1997). Comorbidity may also lead to depression through behavioral pathways such as maladaptive coping, cognitive pathways such as stress and loss of control, or social pathways such as deterioration of social networks (Cohen and Rodriguez 1995).

Conversely, depression may lead to poor adherence (behavioral pathway), biased decisions (cognitive), or deterioration of social networks (social), leading to illness behaviors and physical disorders (Cohen and Rodriguez 1995). For example, poor adherence to antihypertensive medication can lead to stroke or renal failure, while poor adherence to medication for diabetes may lead to cardiovascular events as well as end-organ complications.

This model has been explored in late-life depression in a prospective community-based study that followed 1479 community-resident middle-aged and older adults (Meeks et al 2000). In this study, long-term depressive symptoms had an adverse impact on health; however, in the short term, health had an impact on short-term increases in depressive symptoms, but depressive symptoms had a weaker impact on health.

Summary and Research Agenda

All too frequently, studies that have shown a relationship between depression and outcome have not taken comorbidity into account. Patients with the highest burden of comorbid disease are at the highest risk of long-term mortality and morbidity. Patients with increased comorbidity are also at highest risk for functional deterioration, impaired quality of life, and increased resource utilization. Additionally, patients with more comorbid disease are more likely to be depressed, and more likely to become depressed. The failure to measure comorbidity in studies of depression makes it difficult to determine whether the relationship of depression to long-term outcomes is confounded by comorbidity, potentially leading to an overestimate of the impact of depression on outcomes.

Since patients with the greatest comorbidity may be at higher risk for depressive symptoms and poor outcomes, studies must be designed to avoid the potential confounding that may occur; however, the solution is not to exclude patients with the highest burden of comorbidity, because it is precisely this population that may have the greatest problem with depression.

Thus, interventions to prevent and treat depressive symptoms need to take comorbidity into account. Studies must be designed with appropriate methodology to disentangle the independent impact of interventions and comorbid disease on outcomes. Ultimately, significant new research is needed to determine whether, among patients with the greatest comorbidity, by preventing or treating new depression, functional decline, morbidity and mortality also can be reduced.

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References


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